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Original Article

Effect of Gender on Outcomes After Cardiac Resynchronization Therapy in Patients With a Narrow QRS Complex

A Subgroup Analysis of the EchoCRT Trial

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Background—In EchoCRT, a randomized controlled trial evaluating the effect of cardiac resynchronization therapy (CRT) in patients with a QRS duration of <130 ms and echocardiographic evidence of left ventricular dyssynchrony, the primary outcome (death from any cause or first hospitalization for worsening heart failure) occurred more frequently in the CRT-ON when compared with the control group. In this prespecified subgroup analysis, we evaluated the effect of sex on clinical outcome in EchoCRT.

Methods and Results—In EchoCRT, 585 (72%) of included patients were men. At baseline, male patients had a higher incidence of ischemic cardiomyopathy and longer QRS duration. On uni- and multivariable analysis, no significant interaction was observed regarding sex for the primary or any of the secondary end points. Numerically, a higher all-cause mortality was observed in male patients randomized to CRT-ON versus CRT-OFF on univariable analysis (hazard ratio, 1.83; 95% confidence interval, 1.08–3.12); however, no statistically significant interaction compared with females randomized to CRT-ON versus CRT-OFF was noted (hazard ratio, 0.99; *P* interaction, 0.56). There was no difference in the primary safety end point of system-related complications, including CRT system- and implantation-related events.

Conclusions—The largest hazard for all-cause mortality in EchoCRT was observed in men randomized to CRT-ON; the comparison with women did not reach statistical significance, which may be because of the premature termination of the trial and the limited data. These results suggest that male sex may be a risk factor for harm by CRT in patients with narrow QRS width, an observation which deserves further investigation.

Clinical Trial Registration—URL: https://clinicaltrials.gov. Unique identifier: NCT00683696.

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Key Words: cardiac resynchronization therapy ■ cardiomyopathy ■ female gender ■ heart failure ■ risk factor

Cardiac resynchronization therapy (CRT) has been demonstrated to reduce morbidity and mortality in numerous large clinical trials, and it has become an integral part of contemporary heart failure therapy.[1–3] The inclusion criteria of these trials form the basis of current guidelines, recommending CRT for patients with a severely reduced left ventricular ejection fraction of ≤35%, symptomatic chronic heart failure (CHF), and a QRS complex of ≥120 ms.[4] Because the majority of patients with CHF present with a narrow QRS complex,[5] the EchoCRT trial was designed to investigate the effect of CRT in patients with a QRS duration of <130 ms together with echocardiographic evidence of left ventricular dyssynchrony.[6] The trial was terminated early because of futility, but also indicated an increased risk for all-cause mortality of 81% with CRT in this patient population. The sex distribution, as well as the reason for the overall increase in mortality observed in Echo CRT is presently still unclear.

Sex-specific results of CRT have been suggested by some, but not all, previous studies. For example, the Cardiac Resynchronization–Heart Failure (CARE-HF) study[1] was unable to find a sex-by-treatment interaction, whereas in MADIT (Multicenter Automatic Defibrillator Implantation)-CRT, women experienced a 79% reduction in the primary end point (death or heart failure) when compared with only 28%

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WHAT IS KNOWN

- The EchoCRT trial investigated the effect of CRT in patients with a QRS duration <130 ms and echocardiographic evidence of left ventricular dyssynchrony. It was prematurely terminated due to futility, and it indicated an increased risk for all-cause mortality of 81% with CRT in this patient population.
- Gender-specific responses to CRT have been suggested by some, but not all, prior studies.

WHAT THE STUDY ADDS

- The largest hazard for all-cause mortality in EchoCRT was observed in men randomized to CRT-ON.
- The comparison with women did not reach statistical significance, which may be due to the premature termination of the trial.
- These results suggest that male sex may be a risk factor for harm by CRT in patients with a narrow QRS width.

in men. More recently, pronounced female advantage for CRT effect was seen at shorter (120–150 ms) QRS durations.[7,8]

Whether the lack of benefit for CRT shown in EchoCRT pertains to all patients, or whether male or female patients with a narrow QRS complex and echocardiographic signs of dyssynchrony may derive a benefit (or particularly pronounced harm) from CRT is presently unclear. The current prespecified subgroup analysis was, therefore, performed to assess the effect of sex on clinical outcome in EchoCRT.

Methods

Study Design and Conduct

The EchoCRT study was an investigator-initiated, international, multicenter, randomized clinical trial. The outcome results of the main trial, as well as the methodology have previously been reported.[6] In brief, the trial (sponsored by Biotronik) was designed by the executive committee with support for echocardiographic training and software provided by GE Healthcare. All study results were independently analyzed at the Robertson Center for Biostatistics at the University of Glasgow. Patients were eligible if they had New York Heart Association class III or IV heart failure, a left ventricular ejection fraction of ≤35%, a standard indication for an implantable cardioverter–defibrillator (ICD), optimized medical heart failure therapy, a QRS duration of less than 130 ms, a left ventricular end-diastolic diameter of ≥55 mm, and echocardiographic evidence of left ventricular dyssynchrony as previously defined.[6] After implantation of a Biotronik Lumax HF-T CRT-D system, patients were randomly assigned in a 1:1 ratio to have CRT capability turned on (the CRT group) or to have CRT capability turned off (the control group). Device-implanting physicians were aware of the study-group assignments, but the patients, heart failure physicians, and study personnel completing the follow-up assessments were unaware of the group assignments. The trial protocol was approved by the institutional review board at each participating center, and all subjects provided written informed consent.

End Points

The primary efficacy outcome was the combination of death from any cause or first hospitalization for worsening heart failure.[6] The prespecified secondary outcomes included all hospitalizations for worsening heart failure throughout the study: all-cause mortality, cardiovascular mortality, heart failure mortality, and cardiovascular hospitalization.[6] The primary safety outcome was freedom from CRT-D–related complications at 6 months in the implanted population. Complications were defined as adverse events that require additional invasive intervention to resolve, related to the implanted CRT system, including the device and leads. In addition, system-related complications during the whole trial were analyzed by treatment group.

Statistical Analysis

All analyses were performed according to the intention-to-treat principle. Baseline characteristics were compared with the use of 2-sample t tests and χ^2 (or Fisher exact) tests for continuous and categorical variables, respectively.

Hazard ratios (HRs) for CRT-ON and CRT-OFF with 95% confidence intervals (CIs) were calculated with the Cox proportional hazards models for male versus female patients, including the stratification factor of country in the model. In addition, a multivariable Cox proportional hazards model was performed to account for differences across randomized treatment groups in baseline characteristics between males and females (QRS width, walking distance, quality of life [QOL] as determined by the Minnesota Living With Heart Failure Questionnaire score, sitting diastolic blood pressure, ischemic cardiomyopathy, history of myocardial infarction, history of coronary artery bypass grafting, left ventricular end-diastolic diameter, and diuretic agent use). Interactions between males and females and treatment (CRT=ON and CRT=OFF) were tested for in Cox models that included sex and treatment main effects and interaction terms. Time-to-event curves were estimated with the use of the Kaplan–Meier method. All tests were 2 sided with a P value of <0.05 considered to be significant. Analyses were performed using SAS for Windows version 9.2.

Results

Baseline Characteristics

Metrics at trial entry are summarized in Table 1. Of 809 randomized patients, 224 (27.7%) were females. Male patients had longer QRS complex duration, longer walking distance, slightly higher diastolic blood pressure, larger LV diameters, and more frequently had ischemic cardiomyopathy or related interventions. In contrast, women had worse heart failure related quality of life (QOL) and higher use of diuretics. Other baseline parameters were comparable among the 2 groups.

Efficacy of CRT in Male Versus Female Patients

There was no difference for male versus female patients regarding the overall results of the trial, both unadjusted (Figures 1 and 2) and after multivariable adjustment for differences in baseline characteristics as outlined above (ie, QRS width, walking distance, QOL score, sitting diastolic blood pressure, ischemic cardiomyopathy, history of myocardial infarction, history of CABG, left ventricular end-diastolic diameter, and diuretic agent use; Figure 3). Numerically, however, both the increased hazard of CRT for the primary end point, and especially the mortality end points, seemed to be driven mainly by an increased hazard in male patients. Strikingly, cardiovascular mortality was increased 2.4-fold in male patients (HR, 2.43 [95% CI, 1.27–4.63]; P=0.007 versus HR, 0.97 [95% CI, 0.24–3.93], P=0.97 for the females), albeit with a nonsignificant interaction P value. These observations were paralleled in the Kaplan–Meier analyses and in the multivariable adjusted model (again, however, without significant interaction).

Table 1. Baseline Characteristics

Variable	Females	Males	*P* Value
Age, y	57.5 (13.62)	58.2 (12.38)	0.482
QRS width (ms; site)	102.4 (12.89)	106.3 (12.70)	<0.001
QRS width (ms; core)	102.3 (13.35)	107.1 (12.01)	<0.001
Walking distance (m)	286.7 (120.64)	340.4 (116.84)	<0.001
Quality of life score	54.4 (24.15)	50.0 (24.21)	0.021
NYHA classification			
I	0 (0.00%)	5 (0.85%)	*
II	3 (1.34%)	16 (2.74%)	
III	213 (95.09%)	546 (93.33%)	
IV	8 (3.57%)	18 (3.08%)	
BNP (pg/mL)	225.0 (102.00, 471.00)	251.0 (75.00, 515.00)	0.927
NT-proBNP (pg/mL)	1275.0 (610.00, 2124.0)	1095.5 (449.50, 2408.5)	0.604
Sitting SBP (mm Hg)	117.6 (18.11)	119.3 (19.87)	0.271
Sitting DBP (mm Hg)	71.4 (11.18)	73.3 (12.20)	0.039
BMI, kg/m^2	31.7 (14.80)	30.5 (10.98)	0.212
Ischemic cardiomyopathy	88 (39.29%)	344 (58.90%)	<0.001
MI >3 mo ago	66 (29.46%)	256 (43.76%)	<0.001
PCI >3 mo ago	70 (31.25%)	218 (37.26%)	0.110
CABG >3 mo ago	23 (10.27%)	128 (21.88%)	<0.001
Hypertension	146 (66.06%)	387 (66.61%)	0.884
Congenital heart disease	2 (0.92%)	14 (2.42%)	0.259
Previous ischemic stroke or TIA	27 (12.22%)	69 (11.86%)	0.888
Diabetes mellitus	95 (42.79%)	225 (38.53%)	0.269
Chronic lung disease	40 (18.02%)	109 (18.79%)	0.801
Chronic kidney disease	22 (9.95%)	86 (14.78%)	0.074
LVEF biplane (%)	27.2 (5.39)	26.9 (5.63)	0.477
LV end-diastolic diameter (mm)	64.1 (6.84)	67.3 (7.62)	<0.001
Qualified by Tissue Doppler Imaging and radial dyssynchrony			
Tissue Doppler Imaging only	50 (22.32%)	152 (26.03%)	0.050
Radial strain only	42 (18.75%)	143 (24.49%)	
TDI and radial strain	132 (58.93%)	289 (49.49%)	
Medication at study entry			
ACE inhibitor or ARB	212 (94.64%)	555 (94.87%)	0.896
Aldosterone antagonist	130 (58.04%)	355 (60.68%)	0.492
β-Blocker	216 (96.43%)	566 (96.75%)	0.828
Diuretic agent	206 (91.96%)	492 (84.10%)	0.004

For categorical variables, number and percentage are reported; for continuous variables, mean and SD are reported (except for BNP and NT-proBNP where median and interquartile range are presented). ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index; DBP diastolic blood pressure; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NT-proBNP, N-terminal pro b-type natriuretic peptide; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; TIA, transient ischemic attack; and SBP, systolic blood pressure.

**P* value not reported because of small numbers.

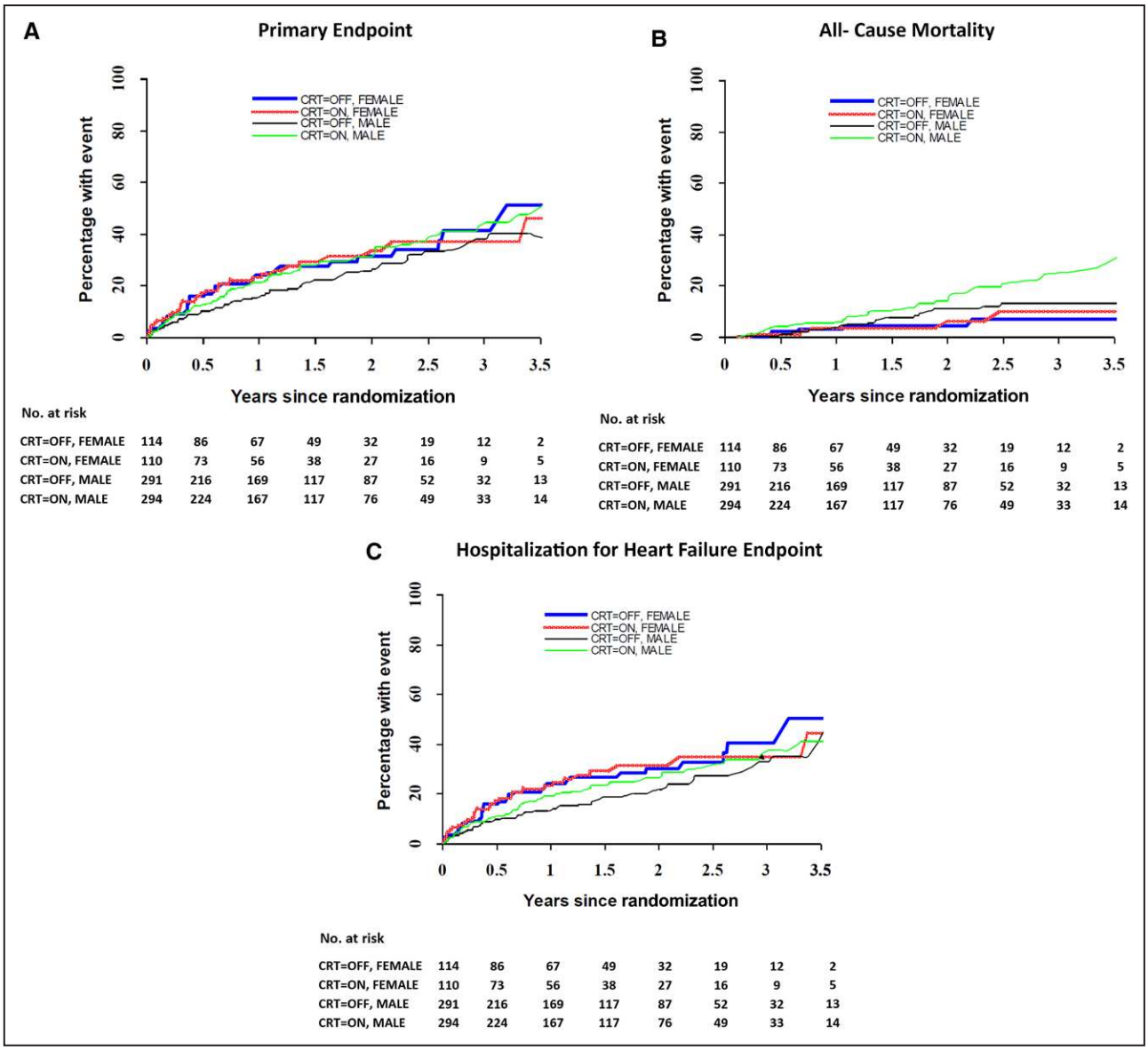

Figure 1. Kaplan–Meier estimates for primary-outcome events, stratified by sex. Kaplan–Meier curves for the primary composite efficacy outcome of death from any cause or hospitalization for heart failure (**A**), as well as the secondary end point all-cause mortality (**B**) and hospitalization for heart failure (**C**) in patients randomized to cardiac resynchronization therapy (CRT)-ON and CRT-OFF, stratified by sex.

Device-Related Complications in Male Versus Female Patients

The primary safety end point (freedom from device-related complications at 6 months) in the implanted population (237 females and 618 males) is presented in Table 2. There were no differences in the primary safety end point, including CRT system- and implantation-related events. Device-related complications occurring during the whole trial in male and female patients are summarized in Table 3. The rate of ICD lead–related complications was numerically higher in women in the CRT-ON group, which was counterbalanced by a numerically lower rate of ICD lead complications in the CRT-OFF group in women (both when compared with men). Overall, the difference between ICD lead–related complications was similar and did not reach statistical significance.

Discussion

In the current prespecified subgroup analysis, a trend indicating a worse outcome for males compared with females can be observed. Indeed, on Kaplan–Meier analysis, the event curve for CRT-ON in women is almost a perfect match to that of CRT-OFF in women as well as in men, possibly indicating a balanced effect (ie, harm in some neutralized by benefit in others). In contrast, male patients seem to be the main driver of worse outcomes of CRT-ON for the entire EchoCRT cohort. The lack of statistical significance may be because of the fact that the trial was prematurely terminated, resulting in a lack of statistical power both for the primary and for the secondary end points, which becomes even more relevant in subgroup analyses. It is tempting to speculate that had the trial been terminated as planned, a statistically significant interaction may have been observed.

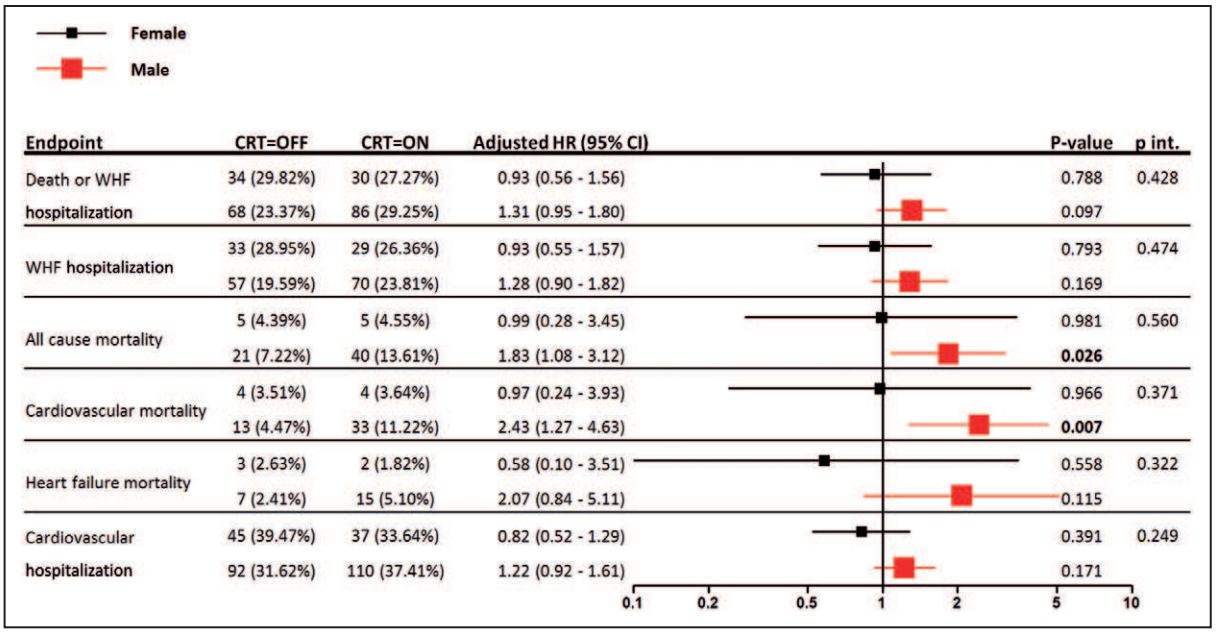

Figure 2. Effect of cardiac resynchronization therapy (CRT) in female (**top**, black) and male (**bottom**, red) patients. Hazard ratio (HR; 95% confidence interval [CI]) adjusted for country and *P* value from Wald test are presented. WHF indicates worsening heart failure.

Our results indicating potential sex-specific differences in CRT effect are consistent with several other large outcome studies, extending those observations to the narrow QRS range studied here. In the early Multicenter InSync Randomized Clinical Evaluation (MIRACLE) Study, women, but not men, receiving CRT had a longer time to first hospitalization for CHF as well as time to first CHF hospitalization or death.[9] In MADIT-CRT, female patients randomized to CRT treatment had a 69% relative risk reduction to experience the primary end point of death or heart failure versus ICD when compared with men, who only had 28% relative risk reduction (*P* interaction <0.001). This effect was driven both by a significant reduction in heart failure hospitalization (70% versus 35% risk reduction) and a significant reduction in all-cause mortality. Indeed, a reduction in all-cause mortality was primarily evident in women (HR, 0.28; 95% CI, 0.10–0.79), but not in men (HR, 1.05; 95% CI, 0.70–1.57; *P* interaction=0.03). A similar trend was also observed in the Resynchronization–Defibrillation for Ambulatory Heart Failure Trial (RAFT), the other large study investigating CRT in oligosymptomatic patients (*P* interaction=0.09).[10] Finally, a large single-center CRT registry found a significant 56%

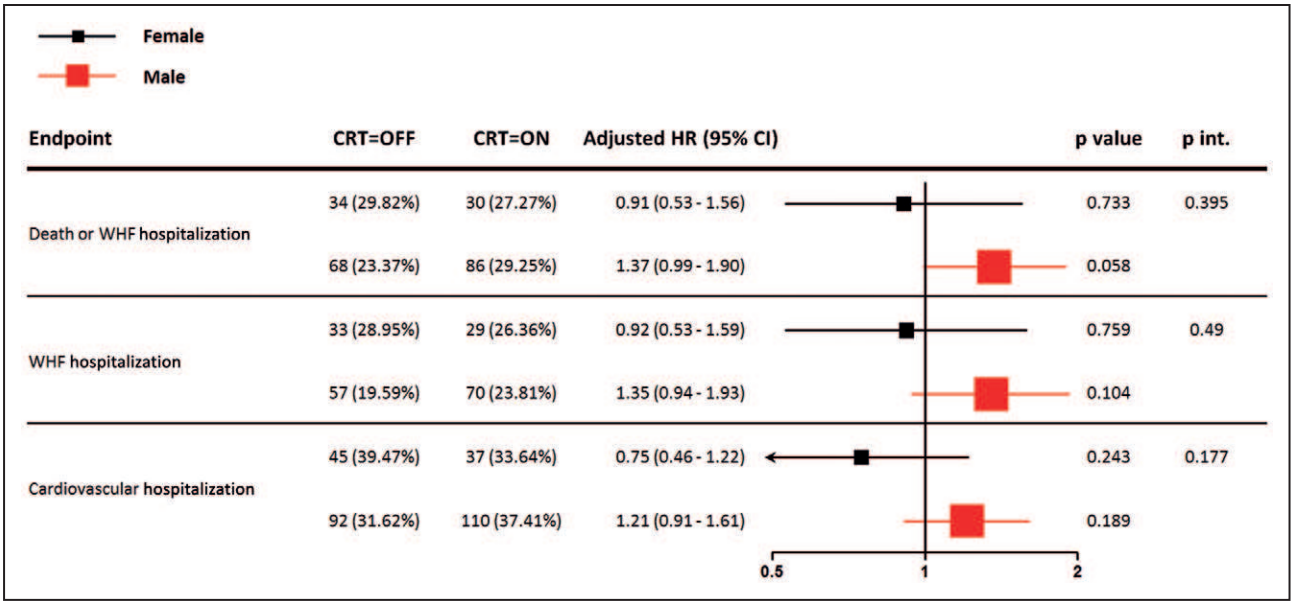

Figure 3. Effect of cardiac resynchronization therapy (CRT) in female (**top**, black) and male (**bottom**, red) patients after multivariable adjustment. Hazard ratio (HR; 95% confidence interval [CI]) adjusted for country, QRS width, walking distance, quality of life score, sitting diastolic blood pressure, ischemic cardiomyopathy, history of myocardial infarction, history of coronary artery bypass graft, left ventricular end-diastolic diameter, and diuretic agent use (*P* value from Wald test). WHF indicates worsening heart failure.

Table 2. Primary Safety End Point in Female and Male Patients (Complication-Free Rate Within 6 Months of Implantation)

	Female Patients (%) Complication-Free (n total=237, %)	Male Patients (%) Complication-Free (n Total=618, %)	*P* Int
CRT-D system	216 (91.14)	569 (92.07)	0.66
Implant procedure	232 (97.89)	605 (97.90)	1
Other	236 (99.58)	617 (99.84)	0.50
Any of the above	210 (88.61)	556 (89.97)	0.56

CRT indicates cardiac resynchronization therapy.

lower all-cause mortality in women compared with men on multivariable analysis.[11] When considered against QRS duration, female advantage (relative to male patients) was most pronounced at shorter (<150 ms) QRS durations.[7] In contrast, some other studies have failed to demonstrate a significant difference between men and women, including CARE-HF.[1] Similarly in the Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) trial, no interaction by sex was observed, although women did have a lower hazard for sudden cardiac death or appropriate shocks.[3,12]

The reason for these differences is just as elusive as the mechanism underlying a potentially more pronounced benefit of CRT in women. Several explanations have been brought forward, including a higher proportion of ischemic cardiomyopathies as well as larger LV diameters in males. Indeed, the latter may play an important role, consistent with a point of no return in the natural course of CHF after which reverse LV remodeling —and, as a consequence, response to CRT—becomes less likely.[13–15] Another hypothesis is related to the difference in QRS duration between men and women. Indeed, in healthy women (as well as in EchoCRT), the QRS duration is on average 4 to 10 ms shorter than that in male patients.[16,17] As a result, male patients with a prolonged QRS complex may have relatively less electric dyssynchrony and intracardiac conduction disturbance for any given absolute QRS duration when compared with women, which may explain the more favorable outcome of CRT in females. Possibly, in shorter QRS ranges as examined here, there is little if any dyssynchrony among males.[18] For these patients, ventricular stimulation itself may be associated with a worse outcome, similar to the development of pacemaker-mediated cardiomyopathy.[19] Indeed, separation of the Kaplan–Meier curve for CRT-ON in males mostly occurs 1.5 to 2 years after implantation, which may indicate a detrimental effect of ventricular pacing on LV function in patients without relevant dyssynchrony, comparable with that of a pacer-mediated cardiomyopathy. In contrast, this phenomenon seems less pronounced in longer QRS durations (ie, >150 ms), after which the relative benefit of male and female patients seems more similar.[7,8] In our subgroup analysis, male patients had larger LV diameters, longer QRS duration, and more frequently had ischemic cardiomyopathy, previous myocardial infarction and previous CABG. Although patients with previous myocardial infarction are generally less likely to respond to CRT[20] or become super-responders,[21] ischemic cardiomyopathy itself has not consistently been associated with a worse outcome in terms of hard end points in any of the major randomized clinical trials.[1,22,23] The sex pattern observed on univariable analysis was still evident after multivariable adjustment, indicating an effect independent of, or at least in addition to those parameters.

In spite of the increasing evidence of a similar, if not more pronounced benefit of CRT in women, CRT remains largely underused in female compared with male patients. In absolute terms, women constitute a large proportion of the population with CHF.[11,24] This is in sharp contrast to the proportion of women included in CRT trials (including EchoCRT), ranging from 17.2% (RAFT) to 32% (COMPANION).[2,3,6] Similarly, CRT remains underused in daily clinical practice, as shown by only 27% females implanted in the EuroCRT survey.[25] Our current analysis cannot readily supply an answer to this phenomenon. A larger concern for complications after device implantation, both from female patients as well as from the referring/implanting physician has been suggested, probably because of smaller vessel diameter and body size.[11,26] In our analysis, the system-/implantation-related complication rate was similar for men when compared with women, indicating that this factor per se should not discourage CRT implants in women.

Limitations

Although prespecified, this subgroup analysis of EchoCRT should by definition be interpreted as hypothesis generating,

Table 3. CRT System–Related Serious Adverse Events During the Whole Trial

	Female Patients				Male Patients				*P* Int
	CRT=ON (n=110)		CRT=OFF (n=114)		CRT=ON (n=294)		CRT=OFF (n=291)		
	N	N Pts (%)	N	N Pts (%)	N	N Pts (%)	N	N Pts (%)	
CRT system related	26	19 (17.27)	7	7 (6.14)	48	36 (12.24)	25	22 (7.56)	0.25
ICD lead	10	9 (8.18)	2	2 (1.75)	16	14 (4.76)	11	11 (3.78)	0.13
RA pacing lead	7	5 (4.55)	1	1 (0.88)	14	13 (4.42)	4	4 (1.37)	0.70
LV pacing lead	7	6 (5.45)	2	2 (1.75)	14	12 (4.08)	2	2 (0.69)	0.57
Implantation related	6	6 (5.45)	3	3 (2.63)	13	11 (3.74)	15	13 (4.47)	0.26

CRT indicates cardiac resynchronization therapy; ICD, implantable cardioverter–defibrillator; LV, left ventricle; N, number of events; N Pts, number of patients with events; and RA, right atrial.

especially because the trial did not meet its primary end point. Sex was not a stratification factor at trial entry leaving the possibility of unmeasured residual confounding. Moreover, the trial was prematurely terminated, further reducing the statistical power of any subgroup analysis. Although the proportion of women included in EchoCRT is in line with other contemporary CRT trials, inclusion of a higher number of women may have increased statistical power for this subgroup analysis.

Conclusions

In the present prespecified subgroup analysis of EchoCRT, a trend indicating a worse outcome for males compared with females can be observed with CRT-ON versus CRT-OFF. This did not reach statistical significance, probably because of lack of power resulting from the premature termination of the trial. These data extend findings from previous large randomized trials and support the use of CRT in female patients if indicated according to the current guidelines. Importantly, these data serve as a reminder to use caution with CRT implantation in men with a narrow QRS complex irrespective of the presence of mechanical dyssynchrony.

Appendix

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Disclosures

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